REMARKS

Status of Claims and Amendment

Claims 33, 35, 41, 55, 59, and 60-64 have been amended. Claims 1-32, 37, and 40 have been canceled. Claims 33-37, 40-42, 53-56, 59, and 60 are all the pending claims being examined in the application. Claims 38, 39, 43-52 and 57-58 are withdrawn as being drawn to a non-elected invention.

Claim 33 has been amended to recite "wherein the PPIase is archaebacterial FKBP-type PPIase." Support for the amendment to claim 33 may be found at least at page 11, line 17 to page 14, line 14 of the specification.

Claim 35 has been amended to recite "wherein the region encodes a protease digestion site in the same reading frame as (a) and (b)" to even further clarify the claimed invention in response to a §112, second paragraph rejection.

Claim 41 has been amended to change the claim dependency to claim 33.

Claim 55 has been amended to recite that the host is "selected from the group consisting of a bacterium, a yeast, a fungus, a plant, an insect cell, and a mammalian cell." Support for the amendment to claim 55 may be found at least at page 26, lines 10-12 of the specification.

Claim 59 has been amended to change the claim dependency to claim 36, as suggested by the Examiner in response to a §112, second paragraph rejection.

Claim 60 has been amended to replace "a host" with "the host cell" as suggested by the Examiner in response to the claim objection. In addition, claim 60 has been amended to recite "under conditions suitable for expression of the expression vector to produce the fused protein in a cytoplasm of said host cell", to even further clarify the claimed invention in response to a §112, second paragraph rejection.

Claim 61 has been amended to correct a typographical error to recite "a 5' terminus of the second coding region of the expression vector." Support for this amendment may be found at least at page 6, line 22 and page 27, lines 8-9 of the specification. In addition, claim 61 has been amended to recite "under conditions suitable for expression of the expression vector to produce the fused protein in a periplasm or a medium of said host cell", to even further clarify the claimed invention in response to a §112, second paragraph rejection.

Claim 62 has been amended to even further clarify the claimed invention by reciting "[a] process for producing a fused protein comprising *in vitro* transcription and translation of the expression vector of claim 36, in a cell-free translation system using a bacteria extract or a eukaryotic extract." Support for the amendment to claim 62 may be found at least at page 27, lines 11-13 and page 28, lines 1-8 of the specification.

Claim 63 has been amended to replace "harboring" with "bound to." Support for the amendment to claim 63 may be found at least at page 24, lines 22-34 and page 28, lines 9-13 of the specification.

Claim 64 has been amended to replace the article "the" with "a" for a fused protein and a protease digestion site, and to replace the article "a" with "the" for the protease digestion site, to even further clarify the claimed invention in response to a §112, second paragraph rejection.

No new matter is added.

Claim Identifiers

The Examiner is thanked for pointing out that the amendment to the claims filed on November 19, 2007 does not indicate those claims withdrawn by the correct identifier.

In response, Applicants have indicated those claims withdrawn by the correct identifier.

Claim Objections

Claim 60 is objected to by the Examiner because "a host" should be "the host cell" in view of the amendments to claim 59 from which claim 60 depends.

In response, Applicants have amended claim 60 to recite "the host cell" as suggested by the Examiner.

Withdrawal of the grounds of objection is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claims 35 and 59-64 are rejected under 35 U.S.C. 112, second paragraph, as being allegedly indefinite.

Claim 35 is asserted to be confusing because of the recitation "encoding a protease digestion site in the same reading frame as the first and second coding regions" since the expression vector of claim 33 does not include a second coding region but a restriction site into which a second coding region may be inserted. The Office Action suggests amending claim 35 to replace "the first and second coding regions" with "the first coding region".

In response, Applicants have amended claim 35 to recite "wherein the region encodes a protease digestion site in the same reading frame as (a) and (b)."

Claim 59 (upon which claims 60-64 depend) is asserted to be confusing because of the recitation "[a] process for producing a fused protein…comprising culturing a host cell transformed with an expression vector of claim 33" since the vector of claim 33 does not include a second coding region fused to the first coding region but a restriction site into which a second coding region may be inserted. The Office Action suggests amending the claim to be dependent on claim 36 which includes the second coding region.

In response, Applicants have amended claim 59 to be dependent on claim 36.

Claim 60 is asserted to be confusing because of the recitation "under condition of expression of the expression vector, and expressing the fused protein in a cytoplasm" as this recitation allegedly is grammatically awkward and confusing. The Office Action suggests replacing this phrase with "under conditions suitable for expression of the expression vector to produce the fused protein in the cytoplasm of said host cell".

In response, Applicants have amended claim 60 as suggested by the Office Action.

Claim 61 is asserted to be unclear because of the recitation "a signal sequence at ... a 3' terminus of the second coding region" since the signal sequences which provide for export into the periplasm or media when fused at the 3' terminus of a protein coding sequence are not known in the art.

In response, Applicants have amended claim 61 to correct a clerical error to recite "a 5' terminus of the second coding region of the expression vector."

Claim 61 is asserted to be confusing because of the recitation "under condition of expression of the expression vector to express the fused protein in the periplasm or a medium" as this recitation allegedly is grammatically awkward and confusing. The Office Action suggests replacing this phrase with "under conditions suitable for expression of the expression vector to produce the fused protein in the periplasm of said host cell or medium of said culture".

In response, Applicants have amended claim 61 as suggested by the Office Action.

Claim 62 is asserted to be confusing because the recitation "culturing a host cell transformed with the expression vector to express the fused protein in a cell-free translation system" is unclear as to how culturing a host cell can be accomplished in a cell-free system. The Office Action suggests replacing the claim with an independent claim reciting production of a

fused protein by a method comprising *in vitro* transcription and translation of the expression vector of claim 36 in a cell-free system.

In response, Applicants have amended claim 62 to recite "[a] process for producing a fused protein comprising *in vitro* transcription and translation of the expression vector of claim 36, in a cell-free translation system using a bacteria extract or a eukaryotic extract."

Claim 63 is asserted to be confusing because the recitation "carrier harboring macrolide, cyclosporine " is unclear since "harboring" is synonymous with "bound or conjugated to" or encompassed by another meaning.

In response, Applicants have amended claim 63 to replace "harboring" with "bound to" to even further clarify that one of ordinary skill in the art would understand from reading the specification, e.g., at page 24, lines 22-34 and page 28, lines 9-13 that the carrier is bound to a compound which inhibits PPIase so that the fused protein may be purified from recovery of the carrier.

Claim 64 is asserted to be confusing because the recitation "which comprises digesting the fused protein comprising the protease digestion site obtained by the process according to claim 59, with a protease digesting a protease digestion site" as there is no protease digestion site in the expression vector of claim 33 (recited in claim 59). The Office Action asserts that the lack of clarity appears to be due Applicants' confusion regarding the previous suggestion by the Office Action to change the phrase "a protease digestion site" in claim 64 to "the protease digestion site". The Office Action asserts that the phrase appears twice in the claim, and Applicants inadvertently changed the wrong one. It is suggested that the claim be amended to recite "which comprises digesting the fused protein comprising a protease digestion site obtained by the process according to claim 59, with a protease digesting the protease digestion site".

In response, Applicants have amended claim 64 as suggested by the Office Action.

Withdrawal of the rejection under §112, second paragraph is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 112, first paragraph

1. Claim 61 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Office Action asserts that the specification does not provide support for the recitation of "a signal sequence at ... a 3' terminus of the second coding region".

In response, Applicants note that claim 61 has been amended to correct a clerical error, and to replace "3' terminus" with "5' terminus." (See page 6, line 22 and page 27, lines 8-9 of the specification).

Accordingly, the rejection is rendered moot.

Withdrawal of the rejection under §112, first paragraph is respectfully requested.

2. Claims 33-37, 40-42, 53-56, and 59-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the same reasons of record.

In addition, the Office Action appears to assert that Applicants' arguments are not persuasive because although it is acknowledged that the art teaches the structures of several PPIases, these known PPIases are not representative of the structure of any PPIase that is currently claimed. The Office Action states that the term "PPIase" is broad including any protein having petidyl-prolyl cis/trans isomerase activity. The Office Action asserts that the PTO written description guidelines require that a claimed genus be sufficiently described by a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical

properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, to show the Applicants were in possession of the claimed genus.

The Office Action asserts that since the genus of PPIases encompasses any protein synthetically or naturally made, the PPIases known in the art and/or disclosed in the specification are not representative of the structure of any PPIase.

Applicants respectfully disagree. In addition to the previous arguments, Applicants note that as explained by the Federal Circuit, "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met…even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Also, what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Applicants note that the structures and functions of PPIases having molecular chaperone activity are well-known in the art, and more than sufficiently described in the specification. As acknowledged by the Office Action at page 7, 2nd full paragraph, "the art teaches the structures of several PPIases."

In the present case, Applicants have provided ample disclosure of the peptidyl-prolyl cis-trans isomerase (PPIase) having molecular chaperone activity, as well as the structures and functions of these proteins which are well-known in the art. For instance, as disclosed at page 10, line 26 to page 11, line 16, the three types of PPIase having molecular chaperone activity are known in the art, i.e., FK506 Binding Protein type (FKBP type), cyclophilin type, and parvulin

type. The structures and functions of these PPIase having molecular chaperone activity are known in the art, and examples are referenced in the specification at page 11, lines 8-16. In addition, other PPIases having molecular chaperone activity are described in the specification from page 11, line 17 to page 18, line 19. All of these PPIase types having molecular chaperone activity and their structures and functions are known in the art. For instance, archebacterial FKBP-type PPIase is known to have a FK506 binding region of a FKBP domain and an IF domain involved in the molecular chaperone activity. (See page 13, lines 11-25 of the specification). Examples of archebacterial FKBP-type PPIase are disclosed at page 12, line 18 to page 13, line 10 of the specification, and SEQ ID NO:2. The structure and function of trigger factor-type PPIase are known in the art (page 14, line 15 to page 15, line 18 of the specification), and the molecular chaperone activity of this type of PPIase is due to action of any or both of its N-terminal and C-terminal (page 15, lines 3-8 of the specification). Examples of trigger factor-type PPIase is disclosed at page 14, lines 16-33 of the specification and SEQ ID NO:3 and SEQ ID NO:4. Another PPIase, SurA-type PPIase, is described in the specification to have a domain having high homology with parvulin-type PPIase on its C-terminal side and the N-terminal side. The specification also teaches that the N-terminal domain of SurA-type PPIase is involved in the molecular chaperone activity. (See page 16, line 30 to page 17, line 2 of the specification). The N-terminal domain of FkpA-type PPIase is known in the art to be involved in the molecular chaperone activity. (See page 16, lines 17-29). Both FkpA-type PPIase and SurA-type PPIase are known as proteins exhibiting molecular chaperone activity. (See page 15, lines 19-29 of the specification). Examples of SurA-type PPIase and FkpA-type PPIase are disclosed at page 15, line 34 to page 16, line 16, and SEQ ID Nos:5-8. Both FKBP52-type PPIase and CyP40-type PPIase (a cyclophilin-type PPIase) are known to have substantially the same function, and it is

also known that the C-terminal domain is involved in the molecular chaperone activity. (See page 17, line 10 to page 18, line 19 of the specification). Examples of FKBP52-type PPIase and CyP40-type PPIase are disclosed at page 18, lines 1-6, and SEQ ID Nos:9-12.

As previously explained, the various species explicitly disclosed for PPIases having molecular chaperone activity in the specification are a sufficient number under current law to provide a representative number of species that are well-known in the art. Teachings of as few as two species are adequate written description to support claims directed to a genus. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F.Supp. 2d 69, 148-149 (D. Mass. 2001), *aff'd in part, vacated in part*, 314 F.3d 1313 (Fed. Cir. 2003) (wherein the Court held that Applicants' disclosure of erythropoietin production in two mammalian cell lines was adequate to inform one of ordinary skill that Applicants' invention encompassed erythropoietin production in any cultured mammalian cell because the claim terms are known to ordinarily skilled artisans).

Thus, PPIase having molecular chaperone activity and their structures and functions are well-known to one of ordinary skill in the art, and described in the specification such that one of ordinary skill in the art would understand that Applicants had possession of the claimed invention at the time the invention was made.

Nevertheless, solely to advance prosecution of the present application, claim 33 has been amended to recite "wherein the PPIase is archaebacterial FKBP-type PPIase."

Claims 37 and 40 have been canceled. Accordingly, the rejection is moot with regard to claims 37 and 40.

Reconsideration and withdrawal of the rejection under §112, first paragraph, is respectfully requested.

2. Claims 33-37, 40-42, 53-56, and 59-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expression vectors comprising a sequence encoding PPIase from *Methanococcus thermolithotrophicus*, *Thermococcus* sp. KS-1, *Methanococcus jannaschii*, *Methanosarcina mazei*, *Methanosarcina acetivorans*, and *Methanosarcina barkeri* and uses thereof, does not reasonably provide enablement for expression vectors comprising a sequence encoding any PPIase having molecular chaperone activity and methods of use thereof.

In addition, the Office Action appears to assert that Applicants' arguments are not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by Applicants (*i.e.*, encoding a PPIase) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. The Office Action asserts that this would constitute undue experimentation. In this regard, the Office Action states that the specification does not establish: (A) regions of the protein structure which may be modified without effecting PPIase activity; (B) the general tolerance of PPIases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any PPIase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Accordingly, the Office Action appears to assert that the claims are not limited to the known PPIase proteins, and the specification does not provide sufficient guidance to enable one of ordinary skill in the art to make the mutant PPIases claimed by Applicants.

Initially, Applicants note that the rejection appears to be based upon limitations that are not recited in the claims, i.e., mutant PPIases. One of ordinary skill in the art would understand from reading the specification and Examples, that the claimed expression vectors and process for making fused proteins are based upon known PPIases having molecular chaperone activity because such PPIases are known in the art to function to refold a denatured protein into an original conformation. Numerous examples of these PPIases are disclosed at pages 8-18 of the specification.

In this regard, Applicants note that the test of enablement is whether one reasonably skilled in the art could make and/or use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. M.P.E.P. 2164.01. In this regard, a patent need not teach, and preferably omits, what is well known in the art. Id. In addition, the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." M.P.E.P. 2164.05(a).

As discussed above, information regarding the structures and functions of PPIases having molecular chaperone activity are known in the art, and amply described in the specification. In particular, the regions responsible for the molecular chaperone activity have been well-elucidated by routine experimentation, and known by one of ordinary skill in the art for PPIases having molecular chaperone activity.

In addition, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. M.P.E.P. 2164.01. As acknowledged by the Office Action, "methods to produce variants of a known sequence such as site-specific mutatgenesis, random mutagenesis, etc. are well known to the skilled artisan." (See page 10, lines 17 of the Office Action). As discussed above in the present case, the structures

and functions of PPIases having molecular chaperone activity are well-known to those of ordinary skill in the art. In particular, the structures of the PPIases have been well-elucidated and known such that the regions responsible for the molecular chaperone activity have been determined for each type of PPIase having molecular chaperone activity by routine experimentation using methods well-known to those of ordinary skill in the relevant art.

Nevertheless, solely to advance prosecution of the present application, claim 33 has been amended to recite "wherein the PPIase is archaebacterial FKBP-type PPIase."

Claims 37 and 40 have been canceled. Accordingly, the rejection is moot with regard to claims 37 and 40.

Reconsideration and withdrawal of the rejection under §112, first paragraph, is respectfully requested.

3. Claim 55 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell transformed with the claimed expression vector, does not reasonably provide enablement for host cells within a multicellular organism that have been transformed with the recited expression vector.

The Examiner asserts that claim 55 broadly encompasses host cells transformed with a specific expression vector including cells in *in vitro* culture as well as cells within a multicellular organism. The Examiner states that the disclosure is limited to only host cells *in vitro*, and Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention within a multicellular organism for production of the claimed polypeptide.

In response, and solely to advance prosecution of the present application, claim 55 has been amended to recite that the host is selected from the group consisting of a bacterium, a yeast, a fungus, a plant, an insect cell, and a mammalian cell.

Reconsideration and withdrawal of the rejection under §112, first paragraph, is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 102

Claims 33-37, 53-56, 59-62, and 64 rejected under 35 U.S.C. §102(a) and (e) as being anticipated by Scholz *et al.* (US PG-PUB 2003/0096352; "Scholz").

The Office Action asserts that Scholz teaches expression vectors for producing a fusion protein comprising a chaperone polypeptide which is a PPIase fused in frame to a protein of interest. The Office Action provides reasons to support this position at page 14 of the Office Action.

In response, Applicants note that Scholz does not explicitly or inherently disclose the presently claimed expression vector wherein the PPIase having molecular chaperone activity is archebaecterial FKBP-type PPIase. Although Scholz teaches FKBP-type PPIase, these are not archaebacterial FKBP-type PPIase.

Reconsideration and withdrawal of the rejection under §102(b) is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 103

Claims 33-37, 40-42, 53-56, and 59-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fersht (WO 00/75346; "Ferst") in view of Furutani *et al.* ("Furutani"), for the same reasons of record.

In addition, the Office Action appears to assert that Applicants' arguments are not persuasive because chaperone activity is not defined as the ability to produce a protein in soluble

form nor do Applicants' claims require that the fusion protein be produced in soluble form. The Office Action asserts that Ferscht teaches that chaperone fragments are any fragment of a molecular chaperone which possesses the ability to promote the folding of a polypeptide *in vivo* or *in vitro*. Thus, the Office Action concludes that Ferscht teaches a vector having a first coding region encoding a fragment of a chaperone that has molecular chaperone activity as defined by the instant specification.

With regard to the 1.132 Declaration of Dr. Ideno, the Office Action asserts that while the Declaration may be sufficient to show unexpectedly superior results of Applicants' exemplified system to one embodiment of the system of Ferscht, any showing of unexpected results is not commensurate in scope with the claimed invention because the present claims are not limited to the TcFk fusion 2 system used.

Applicants respectfully disagree. In addition to Applicants' arguments of November 9, 2007, Fuerst does not teach or suggest the presently claimed expression vector wherein the PPIase having molecular chaperone activity is archebaecterial FKBP-type PPIase.

Furutani does not cure this deficiency. Athough Furutani is directed to an FKBP (FK506 binding protein) from a thermophilic archaeon, *Methanococcus thermolithotrophicus* (see abstract of Furutani), Furutani does not teach or suggest the presently claimed expression vector. Accordingly, even if the teachings of Fuerst and Furutani were combined, the present invention would not be observed.

Thus, it would not have been obvious to one of ordinary skill in the art to combine Fuerst and Furutani to obtain the presently claimed invention.

Furthermore, with regard the 1.132 Declaration of Dr. Ideno, Applicants note that the showing of unexpected results is commensurate with the scope of the presently claimed

invention. Thus, because TcFKPB18 used in the TcKK fusion 2 system is an archebacterial FKBP-type PPIase, the presently claimed archebacterial FKBP-type PPIase shows unexpectedly superior results. In addition, Applicants submit, in a Supplemental Rule 132 Declaration to follow this response, that TcFKBP18 is representative of the claimed archaebacterial FKBP-type PPIase, since any archaebacterial FKBP-type PPIase can show unexpectedly superior results because the PPIase has an IF domain and/or C-terminal domain.

Reconsideration and withdrawal of the rejection under §103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Tu A. Phan/

Tu A. Phan, Ph.D.
Registration No. 59,392

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: May 19, 2008